AMRI Discovery Case Studies

With demonstrated success in all stages of the drug-discovery process, AMRI's capabilities and collaborative approach to discovering pre-clinical nominations and clinical candidates for its customers, embrace the entire drug-discovery platform. AMRI effectively combines *in vitro* biology, drug metabolism and pharmacokinetics (DMPK), computer-aided drug discovery (CADD), synthetic chemistry, and medicinal chemistry to increase the value of customers' drug-discovery programs in an efficient and cost-effective manner.

AMRI scientists have a wide array of experience working with large pharmaceutical and biotechnology companies, as well as non-profit and academic organizations. As a result, AMRI has strength and experience in several therapeutic areas, including anti-infectives, central nervous system disorders, metabolic diseases, oncology, and inflammation. Some of our therapeutic discovery case studies are presented below.

For additional information on how AMRI can help you advance your drug-discovery project, please contact clientservice@amriglobal.com.

Anti-infectives

Case Study: Identification of antibacterial compounds with novel mechanisms of action

- Multi-drug resistant clinical isolates were used to screen AMRI's natural product libraries for samples containing antibiotics.
- Classical antibacterial discovery microbiology and human cell line toxicity assays were used by AMRI to select samples for the purification and structural elucidation of active compounds.
- Optimizations of fermentation conditions and downstream isolation processes were conducted.
- AMRI designed *in vivo* efficacy and pharmacokinetic studies; in-life phases were outsourced to CROs with a reputation for *in vivo* work.
- AMRI designed and conducted mechanism-of-action studies.
- A series of potent, small molecule antibacterial compounds with a novel mechanism of action was identified.
- Series licensed to Genentech in January 2011.

Central Nervous System Disorders

Case Study: Integrated GlyT-1 Inhibitor drug discovery program

- The GlyT-1 transporter was chosen as a target for internally funded R&D.
- AMRI designed and implemented screening strategy, target product profile, and differentiation strategy.
- In-house *In vitro* screening and DMPK assays were integrated with medicinal chemistry efforts.
- Qualified providers designed and implemented *in vivo* models, including those with translational clinical biomarkers.
- Initial hits were obtained from a dual approach using a high-throughput-screening campaign and rational design.
- Through the hit-to-lead process, two lead series were identified – one originating from a high-throughput-screening hit and one from the rational design effort.
- Through lead optimization, AMRI identified a novel series of compounds with excellent selectivity for the transporter and improved potency versus competitor compounds in an animal efficacy model.

Case Study: Lead optimization to identify Central Nervous System drug to treat major depressive disorder

- Medicinal chemistry team performed lead optimization to identify potent triple reuptake inhibitors (of Serotonin, Norepinephrine and Dopamine transporters) suitable for advancement to human clinical trials for treatment of major depressive disorder (MDD).
- Synthesis of more than 2,000 novel compounds has led to the filing of more than 10 patent applications covering composition of matter and chemical method of preparation where AMRI scientists played a major role as inventors.
- Lead compounds were developed and advanced that met the target product profile (TPP) that defined safe and effective lead agents for treatment of MDD.
- Lead compounds and preclinical development candidates demonstrated excellent PK/PD and target engagement data and good safety in animal toxicology studies.
- In the early going AMRI defined a lead optimization screening paradigm and TPP and identified a preclinical development candidate (PDC).
- Simultaneously with AMRI's selection of a PDC, Bristol-Myers Squibb licensed the entire AMRI technology platform and in collaboration with AMRI has progressed three compounds into the development phases.
- BMS 820836 is furthest along in phase II human clinical trials for treatment of MDD.

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AMRI Discovery Case Studies

Oncology

Case Study: Discovery in the identification of preclinical candidates for protein kinase targets

- A multidisciplinary team of AMRI medicinal chemists, *in vitro* biologists, and DMPK scientists worked together to discover preclinical candidates for two protein kinase targets.
- AMRI's *in vitro* biology group developed and validated client's two kinase assays for high-throughput screening. With the new hits from the high-throughput screening, enzyme binding potency was improved 150-fold within the first three months; further optimization led to sub-nM binding activities. 108,000 compounds were screened from AMRI's Diverse Synthetic Library Collection to generate hits.
- U.S.-based medicinal chemistry team prepared 567 compounds, improving enzyme activity about 1000-fold from single-digit micromolar to single-digit nanomolar.
- Supported by CADD and *in vitro* DMPK, the AMRI team improved cell potency greater than 100-fold from single digit μM to single digit nM activity.
- AMRI implemented a compound progression cascade guided by *in vitro* binding and cellular activity data with assays conducted by the client and DMPK data services provided by AMRI – including solubility, permeability, Met Stab, hERG, CYP studies, and bioanalytical studies – to allow medicinal chemists to work in an iterative fashion to effectively progress the program.
- AMRI's CADD team conducted automated docking studies to rank order hits and generated a homology model to understand the observed/measured activity of compounds.
- Modeling studies were conducted to identify potential modifications to the molecules during lead optimization; CADD tools allowed for prioritization of potential targets for future synthesis.
- More than 2,500 compounds have been prepared in this program and more than 10 compounds have demonstrated 30% to 90% tumor growth inhibition *in vivo* upon intravenous dosing on a 14-day efficacy study in nude mice xenograft studies.
- Mouse pharmacokinetic studies have shown two compounds exhibiting greater than 50% oral bioavailability.
- Two patent applications filed with two additional applications expected to be filed.

Inflammation

Case Study: Identification of a Selective Glucocorticoid Receptor Modulator *(SGRM)*

- AMRI developed biochemical, high-throughput screening fluorescence polarization assays to identify compounds to selectively displace the natural ligand from the glucocorticoid receptor.
- AMRI developed cell-based assays using homogeneous time resolved fluorescence and a luciferase-based gene reporter system to identify compounds that could selectively inhibit the expression of inflammatory cytokines, leaving the activities of glucocorticoid response element-mediated pathways unaltered.
- Portions of AMRI's small molecule/natural product sample libraries were screened for SGRMs.
- Natural product actives were purified and their structures elucidated.
- siRNA and shRNA technologies were used to determine if mechanisms of action were dependent on the glucocorticoid receptor.
- Several SGRMs were identified including a 450 pM natural product, non-steroidal SGRM with greater than 50-fold selectivity for transrepression (of inflammatory cytokine expression) over transactivation of glucocorticoid response element-mediated pathways.
- The compound was purified and the structure elucidated.
- The SGRM program progressed to lead optimization.

Metabolic Diseases

Case Study: Fully integrated MCH-1 antagonist drug discovery program

- The MCH-1 antagonist approach was chosen as a target for AMRI's internally funded R&D.
- Screening strategy, target product profile, and differentiation strategy was designed/implemented.
- Hits were generated through a dual approach using a screen of library compounds and through rational compound design and selection using a pharmacophore model.
- Lead optimization drove parameters; e.g. affinity, selectivity, metabolic stability, and *in vivo* activity.
- *In vitro* target assay developed around AMRI proprietary radioligand; *in vitro* DMPK used AMRI platforms.
- AMRI directed design and validation of *in vivo* efficacy/ novel *ex vivo* receptor occupancy assays.
- 1,000 compounds were prepared during lead optimization; multiple compounds progressed into advanced *in vivo* candidate selection studies.
- ALB-127158(a) was chosen as a pre-clinical candidate.
- AMRI guided completion of regulatory safety, toxicity studies, and a Phase I clinical trial.
- Study demonstrated safety/tolerability; second translational Phase I study indicated CNS penetration.
- AMRI identified follow-on compounds as a back-up strategy.